Guidance for Industry

Potassium Chloride Modified-Release Tablets and Capsules: In Vivo Bioequivalence and In Vitro Dissolution Testing

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2002

OGD

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U.S. Department of Health and Human Services
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A.	DISSOLUTION TESTING
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VI	WAIVER OF IN VIVO TESTING FOR LOWER STRENGTHS
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.
- Identify specific comments by line number(s); use the PDF version of the document, whenever possible.

I. INTRODUCTION

This guidance is intended to provide information to sponsors of abbreviated new drug applications (ANDAs) on the design of bioequivalence studies for modified-release dosage forms of potassium chloride. A guidance on this topic was first issued May 15, 1987, and revised June 6, 1994. The May 1987 guidance recommended a single-dose, three-way crossover study. This revision provides recommendations for a two-way crossover design comparing the generic product to the reference listed drug (RLD). In addition, the use of analysis of covariance (ANCOVA), recommended in the original guidance, is no longer recommended. The Agency has determined that analysis of variance (ANOVA) with baseline correction is adequate for bioequivalence analysis of pharmacokinetic data obtained following oral administration of potassium chloride drug products. The in vitro dissolution testing and criteria for waivers of in vivo testing for lower strengths have also been revised to reflect the Agency thinking in the guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*— *General Considerations*, issued in October 2000.

¹ This guidance has been prepared by the Biopharmaceutics Coordinating Committee (BCC) in the Center for Drug Evaluation and Research (CDER) at the FDA.

39 40	п.	BACKGROUND								
41	The p	otassium ion is the principal intracellular cation of most body tissues. Potassium ions participate in a								
42	number of essential physiological processes, including the maintenance of intracellular tonicity, the									
43		nission of nerve impulses, the contraction of cardiac, skeletal, and smooth muscle, and the maintenance								
44		rmal renal function. The intracellular concentration of potassium is approximately 150 to 160								
45		quivalents (mEq) per liter. The normal adult plasma concentration is 3.5 to 5 mEq per liter. An active								
46		ansport system maintains this gradient across the plasma membrane.								
47										
48	Potas	sium is a normal dietary constituent and under steady state conditions the amount of potassium								
49		bed from the gastrointestinal tract is equal to the amount excreted in the urine. The usual dietary intake								
50		tassium is 50 to 100 mEq per day.								
51		· Confidential Confidence								
52	Potass	sium supplements are indicated for the treatment of patients with potassium depletion (hypokalemia)								
53		or without metabolic alkalosis and in digitalis intoxication in patients with hypokalemic familial periodic								
54		vsis. It is also indicated for the prevention of hypokalemia in patients who would be at particular risk if								
55		calemia were to develop (e.g., patients receiving digitalis therapy or patients with significant cardiac								
56	arrhyt	hmias).								
57										
58	Urina	ry potassium measurements are commonly used in studies of bioavailability and bioequivalence.								
59	Becau	ise of the homeostatic mechanisms that maintain serum potassium levels within a relatively narrow range,								
60	serum	levels do not necessarily reflect intake.								
61		om til storf i trof i fram muntfillfir est telfrække fram færende er eg uderskaletiete flyndes, ar egeget i kju Til storf i med en en gjord fram tregte med blevet blevet blevet i skiller i blevet en en en en en en en en en								
52		nost common adverse reactions to oral potassium chloride are nausea, vomiting, flatulence, abdominal								
53	the first of the second of the first	and/or discomfort, and diarrhea. Patients should be instructed to take each dose with a full glass of								
54	water	or other liquid.								
55										
56		entre de la companya de la companya La companya de la co								
57	III.	IN VIVO STUDIES								
58										
59		A. Product Information								
70		and the first of the control of the The control of the control of								
71		1. FDA Designated Reference Product								
72										
73		Potassium chloride for oral administration is marketed as various solid oral dosage forms. Applicants								
74		should consult FDA's Approved Drug Products With Therapeutic Equivalence Evaluations								
75		(Orange Book) for the desired product.								
76		en e								
77		2. Batch Size								
78										
79		The test batch or lot should be manufactured under production conditions and should be of a size at								
30		least 10 percent that of the largest lot planned for production, or a minimum of 100,000 units,								
31		whichever is larger.								
32		a de la composición d La composición de la								
33		. 3. Potency								

84	
85	The assayed potency of the reference product should not differ from that of the test product by more
86	than 5 percent.
87	
88	B. Single-Dose Bioequivalence Study
89	
90	1. Objective
91	
92	The objective of a single-dose bioequivalence study should be to compare the rate and extent of
93	absorption of a generic potassium chloride formulation with that of a reference formulation.
94	그는 그리다는 후보에 하다면 통기가 되었다. (1922년 1일 2012년 1일 12년 1일 12년 1일 12년 1일 12년 1일 12년 12년 12년 12년 12년 12년 12년 12년 12년 1 1월 12년
95	2. Methodology
96	
97	The recommended study design is a two-treatment, two-period, two-sequence crossover. Each
98	subject should receive a single oral dose of potassium chloride at 80 mEq of both the test and
99	reference formulations. Extensive urine sampling for determination of urinary potassium excretion
00	should be performed before and after each dose. Creatinine clearance should be determined to
.01	ensure that urine collection has been adequate.
02	
03	3. Inclusion/Exclusion Criteria
.04	
05	The applicant should include a sufficient number of subjects in the study to demonstrate
06	bioequivalence. Subjects eligible for participation should be between the ages of 20 and 40 years,
07	within ± 10 percent of ideal body weight. Study subjects should be asked not to undertake vigorous
.08	physical exercise beginning 7 days prior to the start of the study period and continuing until discharge
.09	from the clinic. Alcoholic beverages should not be consumed for a period beginning 48 hours prior
10	to drug administration and ending after study completion.
11	는 하는 사람들이 <mark>된 경기에 되는 것이 되었다. 함께 경찰에 함께 되었다. 그 사람들은 경찰에 되었다. 그는 사람들은 사람들은 사람들은 사람들은 사람들은 사람들은 사람들은 사람들은</mark>
12	Subjects with any of the following conditions should be excluded from the study:
13	. 보고 보고 있습니다. 이 이 이번에 있는데 함께 가장 전략적인 함께 하면 되었다. 그는 사람들은 이 생각이 되었다면 하는데 되었다면 하는데 보고 보고 있다. 그는 사람들은 사람들은 사람들이 되었다.
14	Obvious signs of serious renal, gastrointestinal, cardiovascular, hepatic, neurological, or adrenal-
15	pituitary disorders, as evidenced by medical exam, physical exam, and/or clinical laboratory tests
16	
17	• Use of tobacco in any form, currently or within the 6 months prior to study initiation
18	
19	 Use of any known enzyme inducers or inhibitors within 30 days prior to study entry
20	ne di di di dikili da daga a nahagi nakatina pidatan na paka basak basak a salam sikila katina da da da da da
21	History of drug or alcohol abuse
22	- 프로그램 (1915년) 전 12년 1일
23	History of hypersensitivity to the drug or similar compounds
24	
25	• Use of any prescription or nonprescription (OTC) medication within 2 weeks prior to study
26	entry

127

128	Pregnancy, nursing, or failure to use a medically acceptable form of contraception by female
129	subjects
130	
131	4. Dietary and Housing Considerations
132	
133	The subjects should be placed on a standardized diet, with known amounts of potassium, sodium,
134	calories, and fluid. Fluid intake should be maintained at 3,000 to 5,000 ml/day to ensure an
135	adequate rate of urine flow throughout the study period. This is higher than the normal fluid intake of
136	1300 to 2500 ml/day. Strict control and knowledge of the actual intake of potassium, sodium,
137	calories, and fluid are critical for study success.
138	t de la companya de La companya de la com
139	Study subjects should be placed in a climate-controlled environment, remaining in-house as much as
140	possible. Physical activity should be restricted to avoid excessive sweating and thus potassium loss.
141	Detailed information regarding the composition of the diet should be included in the final report.
142	Meals, snacks, and fluids should be given at standard times, and subjects should be strongly
143	encouraged to ingest the recommended amounts and refrain from unnecessary physical activity. In
144	addition, subjects should be queried regarding any prolonged episodes of diarrhea or excessive
145	sweating, as these occurrences may invalidate or obscure the results. A test for fecal occult blood
146	should be performed on each dosing day.
147	er de de la comunitation de destator de de la completa de la completa de la completa de la completa de la comp La completa de la comp
148	5. Collection of Urine and Blood Samples
149	and the second of the second of the space of the second of the second of the second of the second of the second The second of the second of
150	The volume of each urine collection should be recorded. Aliquots of each urine collection should be
151	stored frozen until assayed for potassium. After the aliquots are drawn, all remaining urine samples
152	for each subject over a 24-hour period can be pooled for urine creatinine determination. A blood
153	sample should be drawn at approximately the same time each day for serum creatinine determination.
154	
155	6. Study Design
156	en en en en entre en
157	The study should be conducted over a single period of residence in the clinic, the duration of which is
158	16 days and 17 nights. This should be divided into two periods of 8 days, with dose administration
159	to take place on days 7 and 15. Recommended study procedures are identical for each of the 8-day
160	periods (see Appendix A). The schedule for study periods 1 and 2 follows.
161	and the control of t The control of the co
162	Diet Equilibration Days, Days 1-4 and 9-12
163	and a file-structure of the control
164	 Diets should be standardized to provide the following daily intake of potassium, sodium,
165	and calories:
166	
167	Potassium: 50-60 mEg
168	Sodium: 160-180 mEq
169	Calories: 2500-3500
170	
171	Fluids should be administered according to the following schedule:
172	1 mad strong to manifestating to the following scircular.
	The first that the second of t

173	500 ml of room temperature water initially (at 7:00 hours)
174	200 ml every hour afterwards for 12 hours
175	Additional (known) amounts of fluid can be administered at the investigator's
176	discretion from 19:00 hours until 7:00 hours the following day.
177	사는 사용하다 보는 사람들은 사람들에 가장 보는 사람들이 되었다. 이 사람들이 이 사람들이 이 사람들이 되었다. 이 사람들이 되었다는 것이 되었다는 것이 없는 사람들이 되었다. - 사람들은 사람들이 사용하는 사람들이 가장 보는 사람들이 있다. 사람들이 사람들이 사람들이 사람들이 사람들이 사람들이 되었다. 그 사람들이 사람들이 사람들이 되었다.
178	No urine is collected during the diet equilibration days.
179	u turkurun 1980. Jan Athe milienis Afrikan tib li belinis kentralis beraktelis Belinis kentralis beraktelis berak Dinaman
180	Baseline Days, Days 5-6 and 13-14
181	
182	The standard diet and fluid schedule should continue as described for the equilibration
183	days.
184	and the first of the first of the control of the co
185	 Urine should be collected each day to establish each subject's baseline level of
186	potassium excretion.
187	
188	• Urine collection intervals should be at hours 0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-16 and
189	16-24.
190	
191	 Urine collection should begin at 7:00 hours. On Days 5 and 13, subjects can dispose of
192	this sample. On Days 6 and 14, the urine collected at 7:00 hours completes the 16-24
193	hour sample.
194	
195	 Samples for creatinine clearance determination should be collected on Days 6 and 14.
196	Samples for creating clearance decommation should be conceed on Days v and 14.
197	Drug Dosing Days, Days 7 and 15
198	
199	 After an 8-hour overnight fast, 80 mEq of either test or reference product should be
200	given by mouth at 7:00 hours with 500 ml room temperature water.
201	given by mount at 7.00 hours with 300 lill footh competating water.
202	 Subjects should remain upright (sitting upright, standing, or slowly walking) for at least 3
202	hours following dosing.
204	nous tonowing dosing.
	သည်။ သည် သည် သည် သည် သည် သည် ရေသည် သည်။ သည်သည်။ သည်သည်။ သည် သည် သည် သည် သည် သည် သည် သည်။ သည်။
205	The standard diet and fluid schedule should continue as described for the equilibration
206	
207	and the first of t
208	 Urine collection times should be as on Days 6 and 14.
209	
210	 Samples should be collected for creatinine clearance determination.
211	in transport of the second of the second The second of the second of
212	 Stool samples for determination of fecal occult blood should be collected any time from
213	8 hours post-dosing until the next bowel movement.
214	or or more than 1999 or the second of the se
215	Post-Drug Dosing Days, Days 8 and 16

216	and the control of the control of Alekhard Internation (Alekhard International Alekhard International Alekhard Table 1200 and the control of the Alekhard International Alekhard International Alekhard International Alekhard	
217	• The standard diet and fluid schedule should continue as described for the equilibration	
218	days.	
219	ente de la companya de la companya La companya de la co	
220	 Urine collection times should be as on Days 7 and 15. 	
221		
222	 Samples should be collected for creatinine clearance determination. 	
223		
224	Discharge, Day 17	
225		eli b
226	Subjects can be discharged following the final urine collection at 7:00 hours.	
227	t dat till og det i å, lindt till å. Filå, i bli de åe de ekk å till till till till et dat. Till	
228	7. Clinical Report and Adverse Reactions	
229		
230	Patient medical histories, physical examination reports, and all incidents of possible adverse reaction	IS.
231	should be reported.	
232	entralisment (1975 – 1975). Salake kan terapertuan di beranda periodi di beranda di beranda di beranda di bera Beranda beranda beranda di beranda kaman da di beranda di beranda di beranda di beranda di beranda di beranda d	
233	8. Retention of Samples	
234	and the first of the second of the Million of the second of the second of the second of the second of the second The second of the second o	
235	Retention samples of study drug products must be maintained (21 CFR 320.38), normally at the	
236	testing facility where the study was conducted. The study sponsor should provide the testing facility	7
237	with a sufficient supply of the test and the reference products to complete the study and retain the	
238	appropriate number of dosage units as reserve samples. The study sponsor should not predetermine	
239	the samples to be retained prior to sending the batches to the testing facility. The testing facility will	
240	randomly select the reserve samples from the supply sent by the sponsor. This is to ensure that	
241	reserve samples are in fact representative of the same batches provided by the study sponsor for the	3
242	testing. For more information on retention of bioequivalence samples, please refer to 21 CFR	
243	320.38 and 320.63.	
244 245	مست المستوي وليكون ومعالم في المن المعالم والمستوي المستويد المنافع المنافع المنافع المنافع المنافع المنافع الم المعالم المنافع المنافع المنافع والمنافع المنافع المنافع المنافع المنافع المنافع المنافع المنافع المنافع المنافع	
243 246	IV. DATA ANALYSIS	
247		
248	Baseline excretion of potassium (obtained during the baseline days) should be subtracted from the amount	
249	obtained on the drug dosing day to yield the net effect of drug administration. The baseline data used should	
250	be the average of the two readings obtained on the two baseline days and be subject specific and period	
251	specific (e.g., for subject #12, his period II amount of baseline excretion should only be used to adjust his	
252	period II drug dosing day amount). Although fluctuations in the baseline are expected, differences in baselin	16
253	excretion amounts for the two baseline days should not differ by more than 100 percent.	
254		
255	The following information on urine potassium concentration data should be recorded for each subject:	
256		
257	Amount excreted in each collection interval (Ae)	
258	• Completive prinary excretion from 0-24 hours (Ae0-24h)	
259	그를 하는 사람들이 되었다면 하면 함께 가는 문을 가득하고 어떻게 하면 됐다. 살림, 살림, 생산 생산 생생 사람들이 생각하는 사람들이 하는 것이 되었다. 그는 사람들이 나는 사람들이 나를 하는 사람들이 나를 다 되었다.	
439	Cumulative urinary excretion from 0-48 hours (Ae0-48h)	

260	 Maximal rate of urinary excre 	tion (Rmax)
261	Time of maximal urinary excre	etion (Tmax)
262	Area under the excretion rate	vs. time curve (AUCr = $[{R_1+R_2}*{t_2-t_1}/2]$)
263	Excretion rate in each collecti	
264	Midpoint of each collection in	
265	er en en 1900 en en 1900 en eller flore de floren de la proportion de la florence des la florence de la floren	al territoria de la companya del companya de la companya del companya de la companya del la companya de la comp
266	All data should be calculated using baseling	ne adjusted and non-baseline adjusted data. Statistical analysis (p =
267		eline adjusted parameters, and the 90 percent confidence intervals
268		nontransformed cumulative urinary excretion from 0-24 (Ae ₀₋₂₄)
269	그는 그들은 그리면 가게 되는 것 같아요. 그런 경우 그는 얼마 없는 것 같아 나를 보는 것이다.	(Rmax). The two one-sided tests procedure should be used to
270	determine 90 percent confidence intervals	
271		
272	V. IN VITRO TESTING	adi at 144 likak kecapanyak Panjida salapaga kefitar I Afda menalapaga tendah 145 ke
273		
274	A. Dissolution Testing	
275		are 1960 are some en
276	Dissolution testing should be cond	ducted on 12 individual dosage units from the batches of test and
277	reference products used in the bio	equivalence studies. Early sampling times of 1, 2, and 4 hours
278	should be included in the samplin	g schedule to ensure against premature release of the drug (dose
279	dumping) from the formulation.	The recommended general dissolution conditions are shown below.
280		
281	1. Apparatus	USP 24 Apparatus I (rotating basket) for capsules
282	and the second s	USP 24 Apparatus 2 (paddle) for tablets
283		e de la compressión de la compressión La compressión de la
284	2. Rotation Speed	100 rpm (basket)
285		50 rpm (paddle)
286		
287	3. Temperature	37 □0.5°C
288		
289	4. Units to Be Tested	
290		
291	5. Dissolution Medium	900 ml of de-ionized water
292 293	6 Compliant school la	1.2 About and around 1 11 000/ Cd
293	6. Sampling schedule	1, 2, 4 hours, and every 2 hours thereafter, until 80% of the
295		drug is released.
296	Spacifications for the dissolution	procedure to ensure quality control will be determined on a case-
290 297	by-case basis.	
298	Oy-case dasis.	der der Springerig som filmerskerigt französer i der er en andere er
299	B. Content Uniformity Te	
300	5. Concent Camoranty Te	
301	Content uniformity testing on the	test product lots should be performed as described in USP 24.
302	Conton amounty assuig on the	was product too around to performed as described in OSF 24.
202		

303

304	VI. WAIVER OF IN VIVO TESTING FOR LOWER STRENGTHS
305	
306	Waiver of in vivo bioequivalence study requirements for the lower strengths of a generic product can be
307	granted (21 CFR 320.22(d)(2)) provided the following conditions are met.
308	ette og en trænger i till till til til still kallingt i tre og ette og en bliggere etter til stille og etter t Her og en som en en en en en sæktiger med men sem kallinger fra til ette en ette skriver etter etter en etter
309	• The in vivo study on the highest strength is acceptable and demonstrates that the test potassium
310	chloride product is bioequivalent to the corresponding reference product.
311	and the state of the The state of the sta
312	The lower strengths are proportionally similar in both active and inactive ingredients to the
313	strengths tested in vivo, and have the same drug release mechanism.
314	으로 보고 있는 것이 되는 것이 되는 사람들은 사람들에 가장 전혀 가장 가장 이 생각을 하는 것이 되었다. 그 사람들이 가장 사람들이 되었다. 그 사람들이 되었다. 그 그 그 그 사람들이 되었다.
315	 All strengths meet an appropriate in vitro dissolution test. Dissolution profiles between the
316	highest strength and the lower strengths should be similar, based on the f2 test using the method
317	described previously (V.A) and in three additional dissolution media (e.g., pH 1.2, 4.5, and 6.8).
	- Company of the common of the company of the compa

Appendix A: STUDY SCHEDULE

Bioequivalence Stu	ıdy Sc	hec	lule	fo	r Po	ota	ssiu	ım	Chl	orid	le E	R T	able	ts, (Caps	sule	S	policy and the property of the property of
Activity	Day Days			Days														
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Admit to Clinic	Х													1				
Diet Equilibration		X	X	<	X					X	X	X	X					
Baseline						X	k							X	X			ĺ
Drug Dosing								X								Х		
Post-Drug Dosing									Х								X	
Collect Urine Samples						X	K	X	X					X	X	Х	X	
24 –hr Creatinine Clearance							X	Х	x						Х	Х	X	
Fecal Occult Blood								Х								X		
Discharge																		X

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